



ASSESSING THE EFFECTS OF ORLISTAT AS AN ANTI-OBESITY DRUG IN HIGH FAT DIET INDUCED OBESITY IN MALE RATS

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The present work was designed to evaluate the effectiveness of the orlistat drug on some hormones and biochemical parameters in male rats received a high fat diet (HFD). Twenty-four rats were divided into four groups: 1st group administered normal diet, 2nd group administered HFD, the 3rd group administered HFD plus 9.5 mg/kg b.w./day orlistat, and the 4th group administered HFD diet plus 19 mg/kg b.w./day orlistat. The experimental period was for four weeks. At the end of the experiment, blood samples were obtained for biochemical and hormonal assays. The administration of HFD for four weeks increased significantly the weight gain, serum total cholesterol (TC), triglycerides (TAG), low density lipoprotein (LDL-c), glucose, insulin, triiodothyronine (T3), thyroxine (T4), leptin, with the significant decrease in high density lipoprotein (HDL-c), ghrelin, thyrotropin (TSH) and testosterone hormones in the serum as compared with the control group. The treatment with orlistat neutralized the levels of the measured parameters as compared with HFD fed rats and the results were correlated with the dose of orlistat. In conclusion, an improvement was observed in the biochemical and hormonal results by the treatment with orlistat drug.

INTRODUCTION

Obesity is a chronic disease that results in the accumulation of excess fat in the body due to an energy imbalance. The obesity may be caused by multifactorial etiology, including lifestyle, environment, genetics, metabolism, and behavioral components¹. The factors of lifestyle, such as regular physical activity, proper nutrition and changes in eating behaviors play an important role in combating obesity². Numerous diseases are caused by obesity, including hypertension, hypercholesteremia, sleep apnea, pulmonary hypertension, cardiovascular disease and type 2 diabetes³. Martorell *et al.*, reported that Egypt have the highest proportion of obesity (20.1%)⁴.

Anti-obesity drugs are all pharmacological agents used to reduce or control weight. These medications alter one of the human body essential processes, either by altering appetite or absorption of calories⁵. Excessive fat intake

is a common cause of the development of hyperlipidemia and obesity, a compound that selectively limits the absorption of ingested fat might be useful in both condition treatments⁶. Orlistat is a pharmacological agent facilitating the weight loss and the weight maintenance via inhibiting of pancreatic lipase, an enzyme that is necessary for the triglycerides digestion, it reduces the absorption of fat by 30% through three doses of 120 mg daily⁷. There are no side effects of orlistat due to its lack of absorption⁸. So, we have investigated in the present study the the ameliorating of orlistat on some hormones and biochemical parameters in a high fat diet (HFD) induced animal model of obesity.

MATERIALS AND METHODS

Twenty-four male albino rats weighing (150-160 g) were included in the present research. The rats were obtained from National Organization for Drug Control and Research

farm, Giza, Egypt. Rats were housed in well aerated cages under common and controlled laboratory conditions of relative humidity ($55\pm 5\%$) and temperature ($25\pm 5^\circ\text{C}$), with a natural and 12h/12h light/dark cycle and were provided commercial rodent diet and water *ad libitum* for one week for adaptation.

Composition of normal diet (ND) and high fat diet (HFD)

Two types of diets had been used in the present study, normal diet (ND) for control rats⁹, and high fat diet (HFD) (30%) for induction of the obesity in the rats⁵.

Drug

Orlistat is a potent, specific, irreversible inhibitor of pancreatic and gastric lipases. Also known as tetrahydrolipstatin, it is a chemically synthesized derivative of lipstatin, which is naturally produced by *Streptomyces toxytricini*¹⁰. Orlistat drug was obtained from the pharmacy in Cairo, Egypt. According to the equivalent therapeutic dosages of human-mouse conversion factor¹¹, the dose of orlistat (120 mg/kg b.wt.) was calculated and given for four weeks. The experimented rats were injected orally with orlistat that dissolved in the distilled water at low dose (9.5 mg/kg b.wt.) and a high dose (19 mg/kg b.wt.).

After one week of the adaptation, the animals were divided randomly into four groups ($n=6$ per group) as follows:

- **Group 1 (G1):** Served as a control group in which the rats received NFD for four weeks.
- **Group 2 (G2):** Served as HFD group in which the rats were fed a high fat diet for four weeks.
- **Group 3 (G3):** Rats received HFD and treated orally with a low dose of orlistat (9.5 mg/kg) daily for four weeks.
- **Group 4 (G4):** Rats received HFD and treated orally with a high dose of orlistat (19 mg/kg) daily for four weeks.

Body weight gain

The body weight gains for each rat were recorded before the initiation of the study (Day 0), and at the end of the experiment, then calculated for each group.

Serum biochemical measurements

At the end of the experimental period, the rats were fasted overnight. They were

anaesthetized with diethyl ether and sacrificed by cervical dislocation. Then, the blood samples were collected, part of the blood was used for estimation serum glucose level enzymatically¹², using Spinreact diagnostics kits (Girona, Spain) and the second part of the blood was left to obtain the serum by centrifugation of the blood at 4000 rpm for 10 min and stored at -80°C immediately for further analyses.

Serum total cholesterol (TC), triglycerides (TAG) and high-density lipoprotein cholesterol (HDL-c) were measured by enzymatic colorimetric methods of Allain *et al.*¹³; Buccolo and David¹⁴ and Kostener¹⁵, respectively. Whereas low density lipoprotein cholesterol (LDL-c) was calculated according to Friedewald *et al.*¹⁶, which is (in mg/dL):

$$[\text{LDL-c}] = [\text{TC}] - [\text{HDL-c}] - [\text{TG}/5]$$

Leptin level was determined by the rat leptin ELISA kit (Crystal Chem Inc., USA)¹⁷. ELISA kits for measuring rat serum ghrelin were obtained from Abcam Biochemicals, USA¹⁸.

The insulin serum level was detected using the rat insulin ELISA kit (Crystal Chem Inc., Downers Grove, IL 60515, USA)¹⁹. Free tri-iodothyronine (FT3) and free thyroxine (FT4) serum levels were measured using radioimmunoassay RIA kits (Institute of Isotopes, Budapest, Hungary). Serum thyroid stimulating hormone (TSH) was estimated by using RIA a specific rat TSH kit (supplied by Diagnostic Products Corporation DPC, Los Angeles, USA). Radioactivity was determined by the gamma-counter²⁰. The serum testosterone level was assayed using kits of Hellabio biokits Company (USA) and following the manufacturer's instruction by ELISA radio immunoassay²¹.

Statistical analysis was carried out by a computer program using SPSS program (Version 16)²². The significant differences among groups were determined by one-way analysis of variance (ANOVA). The analysis followed by post hoc test using Duncan test to compare significance between each two groups at $p\text{-value} < 0.05$. Percentage difference (% D) calculated by the following equation:

$$\frac{\text{Treated value} - \text{Control Value}}{\text{Control Value}} \times 100$$

RESULTS AND DISCUSSION

Table 1 shows that the initial body weight revealed a non significant change between all groups. Whereas, the final body weight was significantly increased in a high fat diet (HFD) rats. Also, the data revealed that TC, TAG, LDL-c, LDL-c/HDL-c and TC/HDL-c were significantly increased in HFD group. This was accompanied with a significant decrease in serum HDL-c as compared to control animals (Table 2). Table 3 shows that the daily administration of HFD resulted in a significant

increase in glucose, insulin and leptin serum levels, while ghrelin level was significantly decreased compared to normal-diet fed male rats. According to table 4, HFD induced a marked decrease in the levels of T₃, T₄ and testosterone hormones, along with increasing level of TSH hormone in comparison with the control group.

All the mentioned parameters that measured in the present study were ameliorated to some extent in orlistat treated groups and the treatment revealed a dose-dependent manner.

Table 1: Initial body weight and final body weight in control and treated groups.

	Group 1	Group 2	%	Group 3	%	Group 4	%	P-value
Initial body weight (g)	155 ^a ± 1.2	154 ^a ± 1.4	-0.6	155 ^a ± 1.6	0	155 ^a ± 1.7	0	-
Final body weight (g)	177.4 ^a ± 1.7	252.6 ^b ± 2.2	42.4	213.8 ^c ± 1.3	20.5	203.4 ^d ± 1.5	14.7	*

Means values + S.E. within the same column having different letters are significantly different means p-value < 0.05. Same letters indicate non significant changes.

Table 2: TC, TAG, HDL-c and LDL-c levels in control and treated groups.

	Group 1	Group 2	%	Group 3	%	Group 4	%	P-value
TC (mg/dl)	82 ^a ± 1.5	144.33 ^b ± 1.9	76	103.8 ^c ± 1.9	26.6	88.83 ^d ± 1.1	8.3	*
TAG (mg/dl)	63.2 ^a ± 1.3	98 ^b ± 2.2	55.1	82.5 ^c ± 1.8	30.5	74.2 ^d ± 1.7	17.4	*
HDL-c (mg/dl)	48.2 ^a ± 3.4	37.83 ^b ± 0.7	-21.5	43.7 ^c ± 1.14	-9.3	48.33 ^a ± 0.9	0.3	*
LDL-c (mg/dl)	21.2 ^a ± 2.4	85.1 ^b ± 4.9	302.8	43.66 ^c ± 1.7	106	25.7 ^d ± 1.1	21.23	*

Means values + S.E. within the same column having different letters are significantly different means p-value < 0.05. Same letters indicate non significant changes.

Table 3: Glucose, insulin, leptin and ghrlin levels in control and treated groups.

	Group 1	Group 2	%	Group 3	%	Group 4	%	P-value
Glucose (mg/dl)	88 ^a ± 2.02	154.5 ^b ± 2.9	75.6	124 ^c ± 1.9	41	105.2 ^d ± 1.8	19.5	*
Insulin (pg/ml)	1.6 ^a ± 0.1	3.7 ^b ± 0.1	131.1	2.6 ^c ± 0.13	62.5	2.2 ^d ± 0.1	37.5	*
Leptin (ng/ml)	3.9 ^a ± 0.1	7.5 ^b ± 0.12	92.3	6.1 ^c ± 0.1	56.4	5.03 ^d ± 0.1	29	*
Ghrlein (ng/ml)	0.9 ^a ± 0.1	0.5 ^b ± 0.043	-44.4	0.7 ^c ± 0.04	-22.2	0.8 ^{ac} ± 0.1	-11.1	*

Means values + S.E. within the same column having different letters are significantly different means p-value < 0.05. Same letters indicate non significant changes.

Table 4: T₃, T₄, TSH and testosterone hormones levels in control and treated groups.

	Group 1	Group 2	%	Group 3	%	Group 4	%	P-value
T ₃ (ng/L)	1.5 ^a ± 0.04	0.9 ^b ± 0.03	-40	1.23 ^c ± 0.03	-18	1.4 ^a ± 0.04	-6.7	*
T ₄ (ng/dl)	2.7 ^a ± 0.1	1.8 ^b ± 0.1	-33.3	2.13 ^c ± 0.1	-21.11	2.44 ^d ± 0.1	-9.6	*
TSH (uIU/ml)	0.5 ^a ± 0.02	0.7 ^b ± 0.022	40	0.53 ^c ± 0.014	6	0.5 ^{ac} ± 0.02	0	*
Testosterone (ng/ml)	1.5 ^a ± 0.06	0.9 ^b ± 0.06	-40	1.2 ^c ± 0.1	-20	1.4 ^{ac} ± 0.1	-6.7	*

Means values + S.E. within the same column having different letters are significantly different means p-value < 0.05. Same letters indicate non significant changes.

All Tables

The incidence of obesity is progressively rising worldwide and reaching epidemic proportions in some countries²³. The current study aimed to evaluate the impact of obesity development on the indices of some biochemical parameters and certain hormones of male albino rats and the probable protective effects of the orlistat as anti-obesity drug on these parameters. Orlistat is a weight-loss drug with minimal systemic absorption²⁴, and therefore any effect of this drug is a result of weight loss and not a direct effect on the body. In this work, feeding rats with a high fat diet (HFD) has been used to develop experimental obesity in male rats. The present data revealed a hyperlipidemia, hyperglycemia and hyperinsulinemia and were characterized by the

elevated weight gain, total cholesterol (TC), triglycerides (TAG), low density lipoprotein LDL-c, glucose, insulin, T₃, T₄ and leptin levels, with a significant decrease in HDL-c, ghrelin, TSH and testosterone hormones in the serum as compared with control group. These results are in harmony with previous researches^{25&26}, which demonstrated that diets containing a high proportion of saturated fatty acids resulted in elevated the plasma concentrations of TC and LDL Cholesterol. Also, the present elevated serum insulin level in the obese rats as compared with the corresponding controls were in accordance with that Abdel-Nabi *et al.*²⁷. A selective hepatic insulin resistance, a hallmark of obesity, is manifested by a failure to inhibit gluconeogenesis²⁸. So, the hyperglycemia and

hyperlipidemia that were recorded in the present study may be attributed to the hepatic insulin resistance induced by HFD²⁹. Since, free fatty acids (FFA) released from fat deposits, especially visceral fat, can block the insulin signal pathways directly and thus interrupt insulin action³⁰. Also, consistent with the present results, a HFD has been shown to cause weight gain in the rats, mild hyperglycemia, hyperinsulinemia and impairment in blood glucose regulation, hypertriglyceridemia, hypercholesterolemia³¹.

Treatment of obese rats with the orlistat improved the previous results towards the normal control levels. The improvement resulted from therapy with orlistat may be attributed to its effect on the body's ability to absorb dietary fats³², and the reduction of the enzymatic activity that mediated through the covalent binding of orlistat to the serine residue of the lipase active site³³. Orlistat was used as a positive control because of its effectiveness in managing weight by reducing leptin levels and fat mass³⁴. Orlistat changes the amount of fat delivered to the liver as well as the type of fat, thereby modulating insulin action to reduce the absorption of dietary fat³⁵.

Our results revealed that the circulating level of the anorexigenic hormone leptin is increased, whereas surprisingly, the level of the orexigenic hormone ghrelin is decreased in response to a HFD compared with the control rats. These findings are in agreement with various studies Venner *et al.*³⁶ and Antunes *et al.*³⁷. These findings indicated that obesity is a state of leptin resistance. Leptin resistance has been shown to exist in obese human patients, who are hyperphagic but have very high serum leptin levels³⁸.

Concerning with the testosterone hormone level in this study, the results were in concordance with observed a reduction in testosterone levels in Sprague-Dawley rats fed a HFD from weaning at 90 days³⁹. The reduction in testosterone level in the obesity rats may be attributed to transform of testosterone into estrogen which decreases testicle stimulation⁴⁰, or may be due to the induction of induces lipid metabolic disorder by a HFD as reported by the results of this work and leads to a loss of male reproductive function, such as low serum testosterone level,

sexual hormones metabolic changes, several adverse reproductive outcomes⁴¹.

A significant decrease in the level of FT₃ and FT₄, while a significant increase occurred in the level of TSH hormone were reported in the present obese rats comparing with the control ones. These results seemed to be in complete accordance with earlier studies⁴². These results may be attributed to the disturbance in hypothalamus-pituitary axis, the conversion of FT₃ to FT₄ or/and conversion of reverse FT₃ to FT₄ as a result of feeding rats on a HFD causing hypothyroidism. So, the thyroid disorders might participate in the pathogenesis of obesity.

It could be suggested that the ability of orlistat to ameliorate the testosterone level and thyroid functions may be attributed to modulating the action of insulin and lipid metabolism. This suggestion need more studies to support it.

On the basis of the present results, we concluded that the disturbance that occurred in the levels of some biochemical parameters and certain hormones in obese rats induced by a high fat diet could be ameliorated by the orlistat administration and the treatment was correlated with the dose used.

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نشرة العلوم الصيدلانية جامعة أسيوط



تقييم تأثير الأورليستات كعقار مضاد للسمنة على السمنة المستحثة بنظام غذائي عالي الدهون في ذكور الجرذان

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تهدف الدراسة الحالية الي تقييم فعالية عقار الأورليستات على بعض الهرمونات والمعايير البيوكيميائية في ذكور الجرذان التي تلقت نظام غذائي عالي الدهون. لقد تم تقسيم أربع وعشرون جرذاً إلى أربع مجموعات: المجموعة الأولى (الضابطة) تناولت نظاماً غذائياً عادياً ، والمجموعة الثانية تناولت نظام غذائي عالي الدهون ، والمجموعة الثالثة تناولت نظام غذائي عالي الدهون بالإضافة إلى ٩,٥ ملجم/كجم من وزن الجسم/يوم أورليستات ، والمجموعة الرابعة تناولت نظام غذائي عالي الدهون بالإضافة إلى ١٩ ملجم/كجم من وزن الجسم/يوم أورليستات واستمرت التجربة أربع أسابيع. تم عمل القياسات البيوكيميائية والهرمونية لعينات الدم في نهاية التجربة. ووجد أن تناول الجرذان لنظام الغذائي عالي الدهون لمدة أربعة أسابيع أدى إلى زيادة ملحوظة في زيادة الوزن ، والكوليسترول الكلي في الدم (TC)، والدهون الثلاثية (TAG)، والبروتين الدهني منخفض الكثافة (LDL-c)، والجلوكوز ، والأنسولين ، وثلاثي يودوثيرونين (T3) ، هرمون الغدة الدرقية (T4) ، الليبتين ، مع انخفاض ملحوظ في البروتين الدهني عالي الكثافة (HDL-c) ، الجريلين ، الثيروتروبين (TSH) وهرمونات التستوستيرون في المصل بالمقارنة مع المجموعة الضابطة. وأدت المعاملة بعقار الأورليستات إلى الرجوع للمستوي الطبيعي في المعاملات المقاسة مقارنة بالجرذان التي تناولت غذاء عالي الدهون وكانت النتيجة مرتبطة بالجرعة المستخدمة لعقار الأورليستات. لقد توصلت هذه الدراسة الي أن استخدام عقار الأورليستات أدى الي تحسن في النتائج البيوكيميائية والهرمونية للجرذان.